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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/847,945 | 05/02/2001 | Neil P. Desai | 638772000127 | 6174 |

25226 7590 03/17/2011

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| EXAMINER | |
|---|---|
| CHANNAVAJJALA, LAKSHMI SARADA | |
| ART UNIT | PAPER NUMBER |
| 1611 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 03/17/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficePA@mofo.com
drcaldwell@mofo.com
PatentDocket@mofo.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/847,945 | DESAI ET AL. | |
| | Examiner | Art Unit | |
| | LAKSHMI CHANNAVAJJALA | 1611 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3-5,7-14,17,31-55,57,59,60,62-70,72-84 and 94-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-14,17,31-55,57,59,60,62-70,72-84 and 94-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-22-10*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Receipt of RCE, amendment, remarks and IDS all dated 12-22-10 is acknowledged.

Claims 2, 6, 15-16, 18-30, 56, 58, 61, 71, and 85-93 are cancelled.

Claims 1, 3-5, 7-14, 17, 31-55, 57, 59-60, 62-70, 72-84 and 94-96 are pending.

***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/22/10 has been entered.

The following rejections of record have been maintained:

## *Claim Rejections - 35 USC § 103*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 57, 59-60, 62-70, 72-84 and 91-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Kunz et al (5,733,925) in further view of Westesen et al (6,197,349).

Desai et al teach an anticancer (antineoplastic) drug, specifically taxol derivatives such as **paclitaxel**, is suspended in a protein walled shell. See abstract. The shell is not greater than about 10 microns, preferably less than 5 microns, and most

preferably less than 1 micron (1000 nanometers). See column 5, lines 30-40. For intravenous administration, the particles may have a diameter size from 0.1-5 microns. See column 9, lines 15-16. Desai teaches the method of delivery for the instant particles allows the administration of substantially water insoluble pharmacologically active agents employing a much smaller volume of liquid and requiring greatly reduced administration time relative to administration volumes and times required by prior art delivery systems (e.g., intravenous infusion of approximately one to two liters of fluid over a 24 hour period are required to deliver a typical human dose of 200-400 mg of taxol). See column 3, line 60 to column 4, line 5.

The particles may be formed using biocompatible polymers, proteins, or polysaccharides. A preferred protein for the shell is albumin. See column 6, lines 40-45 and example 4. Taxol exhibits a unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. See column 1, lines 20-30. Desai teaches administration of the microparticulates are advantageous in targeting specific sites in the body; allows for the administration of water-insoluble actives; reduces administration time. See column 3, lines 60-67 to column 4, lines 1-5. The particles also are stable and low in toxicity. See examples 5 and 7. Example 8 teaches injecting the particles in a ten-minute period.

Desai does not specify the instant methodology of treating non-cancerous cell proliferation in blood vessels. Further, Desai does not teach an amorphous drug.

Kunz et al teach methods for **inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells.** Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz teaches protein-coated particulates. See column 25, line 20 to column 26, line 40. Therapeutic agents such as **taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell.** Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .001 to 100 mg/kg per day. See column 28, line48. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a single pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents

may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment. Kunz teaches single administration protocol. See column 36, lines 50-55. Example 6 teaches infusion using a balloon catheter. Administration to a carotid, femoral, and coronary artery is taught. See examples. Example 3 teaches administering the dose in less than three to five minutes. Also note example 5 and 14.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated drug (antineoplastic drug taxol) for the treatment of proliferation of non-cancerous cells in blood vessels (restenosis). One would have been motivated to do so since Kunz teaches inhibiting stenosis following vascular trauma, diseases resulting from hyperactivity or hyperplasia of somatic cells using cytotoxic drugs such as taxol or analogs. Kunz teaches taxol or its analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing to reduce atherosclerosis or restenosis since taxol promotes the formation of usually stable microtubules inhibiting the normal dynamic reorganization of the microtubule network

required for mitosis and cell proliferation. Furthermore, Desai et al also recognize taxol's unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. Therefore, one would have expected success by utilizing Desai's taxol to treat abnormal proliferation in the blood vessels since Kunz teaches taxol is an effective drug that prevents or reduces cell proliferation in the blood vessels.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Desai since both are directed to poorly water-insoluble drugs.

With respect to the claim limitation that the nanoparticles have an average diameter of no greater than about 200 nm, instant claims recite less than about 200 nm, without defining the term "about". On the other hand, Desai teaches particles of less than 1000 nm and therefore it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to employ an appropriate nanoparticle size of paclitaxel of Desai, because Desai suggests most preferably less than 1000 nm such as 0.1 microns (100 nm) (col. 9, l 15-165) such that the drug is effective and also the administration time is reduced.

***Response to Arguments***

Applicant's arguments filed 12/22/10 have been fully considered but they are not persuasive. Applicants submitted that the arguments presented in previous response (1/12/09 and 10/1409) are incorporated herewith. Applicants' arguments of 1/12/09 have been addressed in the Final rejection of 4/14/09 and accordingly are incorporated in this action.

Applicants argue that instant claims have now been amended to recite that the average diameter of the particles is no greater than 200 nm. It is argued that the methodologies disclosed in Kunz were developed to specifically address the issues of delivering large number of molecules, targeting the drug to intracellular target and optimize the association of drug with its intracellular target with minimum redistribution, suggesting that the drug is administered over several weeks. It is argued that a skilled artisan would not use the particles of Desai to practice the method of Kunz. Applicants argue that the particles less than 2 microns will be cleared rapidly from the RES or MPS systems.

Applicanst' arguments are not persuasive because the rejection is not over Desai alone or Kunz alone and instead over the combination of Desai, Kunz and Westesen. In the instant case, not only Desai but Kunz also suggests the use of nanoparticulate dosage form (col. 4, l 23-25 & col. 14, l 40-50). Thus, the argument that the nanoparticles (<2microns) are cleared rapidly is not persuasive because Kunz suggests effective use of nanoparticles for treating hyperplasia of non-cancerous cells. With

respect to the administration over several weeks, Kunz suggests both loading a small dose for a long time or a large dose in a short time (col. 29, l -126; col. 33). Therefore a skilled artisan would have been able to optimize the time of administration depending on the dose administered. In this regard, applicants argue that the particles of Desai are not expected to reach high enough local concentrations of drug. However, given the preference of Kunz for nanoparticle drug dosage forms, a skilled artisan would have expected to provide the desired local concentration of the drug and hence the treatment fro vascular hyperplasia. Applicants' argue Westesen does not cure the deficiencies of Kunz and Desai. However, as explained in the rejection, Westesen has been cited to show that amorphous drug improves solubility and absorption. With respect to the argument regarding the unexpected results of Exhibit A and examples 7-18 of the instant application, applicants have not described in the instant examples any specific particle size of paclitaxel and hence the results shown are commensurate with the scope of the instant claims.

Instant rejection have provided references that teach taxol derivatives coated with proteins (Desai) and the use of paclitaxel for treating non-cancerous hyperplasia (Kunz) and further employing amorphous drugs for better dissolution and bioavailability (Westesen). Desai, similar to the instant invention, also recognizes the effects of taxol on microtubular function of the smooth muscle cells. While the instant method is neither anticipated not rendered obvious by Desai alone, the claimed invention is obvious in light of the combined teachings of Desai, Kunz and Westesen. In response to applicant's argument, the examiner recognizes that obviousness can only be

established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to employ the composition for treating non-cancerous hyperplasia comes from the teachings of Kunz, who suggest treating stenosis following vascular trauma or diseases resulting form hyperplasia of somatic cells such as smooth muscle cells with cancer treating compounds such as taxol or its derivatives; and Westesen teaches amorphous form of the drug (poorly soluble drug) for better solubility and availability.

Applicants argue that the reduced administration time in the teachings of Desai is to obviate the need for toxic solvents, such that small volumes may be administered, but fails to treat hyperplasia of non-cancerous cells in a blood vessel and lacks amorphous drug form. It is argued that even though the composition of Desai can be administered at a reduced time relative to those required in the prior art without incurring toxicity, Desai by no means suggests that such administration regime would provide high enough local drug concentration for a sustained period of time and allow effective treatment of hyperplasia of non-cancerous cells in the blood vessel. Applicants' arguments are not persuasive because if a prima facie case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case. See, e.g., In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). In the instant case, applicants did not provide

any evidence that the composition of Desai does not result in the high enough local drug concentration for a sustained period of time and allow effective treatment of hyperplasia of non-cancerous cells in the blood vessel, when combined with Kunz and Westesen.

Thus, it is the examiner's position that Desai in view of Kunz and Westesen render the instant invention prima facie obvious.

**Claims 1, 3-5, 7-14, 17, 31-36, 38-43, 46-51, 54-55, 57, 59-60, 62-70, 72-84 and 91-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Hunter et al (5,716,981) in further view of Westesen et al (6,197,349).**

Desai et al teach an anticancer (anti-neoplastic) drug, specifically taxol derivatives such as **paclitaxel**, is suspended in a protein walled shell. See abstract. The shell is not greater than about 10 microns, preferably less than 5 microns, and most preferably less than 1 micron (1000 nanometers). See column 5, lines 30-40. For intravenous administration, the particles may have a diameter size from 0.1-5 microns. See column 9, lines 15-16. Desai teaches the method of delivery for the instant particles allows the administration of substantially water insoluble pharmacologically active agents employing a much smaller volume of liquid and requiring greatly reduced administration time relative to administration volumes and times required by prior art delivery systems (e.g., intravenous infusion of

approximately one to two liters of fluid over a 24 hour period are required to deliver a typical human dose of 200-400 mg of taxol). See column 3, line 60 to column 4, line 5.

The particles may be formed using biocompatible polymers, proteins, or polysaccharides. A preferred protein for the shell is albumin. See column 6, lines 40-45 and example 4. Taxol exhibits a unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. See column 1, lines 20-30. Desai teaches administration of the microparticulates are advantageous in targeting specific sites in the body; allows for the administration of water-insoluble actives; reduces administration time. See column 3, lines 60-67 to column 4, lines 1-5. The particles also are stable and low in toxicity. See examples 5 and 7. Example 8 teaches injecting the particles in a ten-minute period.

Desai does not teach the instant methodology of treating non-cancerous cell proliferation in blood vessels. Further, Desai does not teach an amorphous drug.

Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such **as paclitaxel, epothilone,** and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as **albumin**, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter

teaches the use of the composition to **treat non-tumorigenic angiogenesis dependent diseases.** See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter teaches methods of eliminating vascular obstructions in arteries and veins to prevent recurrent stenosis **(restenosis)** at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and cornary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intarticularly, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent. Example 7 teaches inserting the stent is into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a

substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to utilize Desai's protein coated drug (anti-neoplastic drug taxol) for the treatment of proliferation of non-cancerous cells in blood vessels (restenosis). One would have been motivated to do so since Hunter teaches treating non-tumorigenic angiogenesis dependent diseases including inhibiting stenosis following vascular trauma and neointimal hyperplasia using cytotoxic drugs such as taxol or analogs and epothilone. A skilled artisan would have reasonably expected success since Hunter teaches these therapeutic agents that disrupt microtubule function and thus treat such diseases and Desai et al also recognize taxol's unique mode of action on microtubule proteins responsible for the formation of the mitotic spindle. Therefore, it would have been prima facie obvious to utilize Desai's taxol to treat abnormal proliferation in the blood vessels since Hunter teaches taxol is an effective drug that prevents or reduces cell proliferation in the blood vessels.

Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs. Moreover, one would reasonably expect success by applying Westesen's teachings to Desai since both are directed to poorly water-insoluble drugs.

With respect to the claim limitation that the nanoparticles have an average diameter of no greater than about 200 nm, instant claims recite less than about 200 nm, without defining the term “about”. On the other hand, Desai teaches particles of less than 1000 nm and therefore it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to employ an appropriate nanoparticle size of paclitaxel of Desai, because Desai suggests most preferably less than 1000 nm such as 0.1 microns (100 nm) (col. 9, l 15-165) such that the drug is effective and also the administration time is reduced.

***Response to Arguments***

Applicant's arguments filed 12/22/10 have been fully considered but they are not persuasive. Applicants submitted that the arguments presented in previous response (1/12/09 and 10/1409) are incorporated herewith. Applicants' arguments of 1/12/09 have been addressed in the Final rejection of 4/14/09 and accordingly are incorporated in this action.

Applicant arguments regarding Desai and Westesen have been addressed above. Applicants argue that Hunter does not cure the deficiencies of Desai and Westesen because Hunter teaches a general statement that the antiangiogenic compositions may be prepared for different routes of administration, including intravenous, without any guidance for choosing a particular regime.

Applicants' argument is not persuasive because a reference is considered in its entirety. Hunter teaches administration intrarticularly, intraocularly, intranasally, intradermal, sublingually, orally, topically, intravesically, intrathecally, topically, intravenously, intraperitoneally, intracranially, intramuscularly, and subcutaneously to the disease site. See column 38, lines 1-10. Applicants' arguments that Hunter generally teaches the above routes is not persuasive because Hunter describes the various routes of administration and choosing an appropriate route so as to achieve the desired release of a drug would have been within the scope of a skilled artisan. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Further, it would have been obvious for one of an ordinary skill in the art to try to administer the drug by different routes of administration. Hunter clearly teaches the use of paclitaxel in treating hyperplasia and the administration of paclitaxel nanoparticle in a protein shell by intravenous method comes from Desai.

**Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al (5,439, 686) in view of Kunz et al (5,733,925) or Hunter *respectively* in view of Westesen et al (6,197,349) in further view of Gregory (Transplantation, vol. 59, pp. 655-661, 1995).**

The teachings of Desai, Kunz, Hunter, and Westesen have been discussed above. Desai teaches the use of immunosupressants. See column 5, lines 60-63.

The references do not teach the specific use of rapamycin.

Gregory teaches rapamycin is an immunosuppressant, which has an antiproliferative action that is useful in the treatment of arterial thickening after injury such as angioplasty. See page 655.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and further use rapamycin to treat restenosis. One would have been motivated to do so with a reasonable expectation of success since Gregory teaches rapamycin is an immunosuppressant, which has an antiproliferative effect and thus is useful in treating restenosis. Therefore, a skilled artisan would have been motivated to further utilize rapamycin for its additive effect in treating restenosis.

***Response to Arguments***

Applicant's arguments filed 12/22/10 have been considered but not found persuasive. Applicants argue that Gregory teaches rapamycin but fails to cure the deficiencies of the above references. However, the arguments regarding Hunter, Desai, Kunz and Westesen have been addressed above. Since applicants did not argue the teachings of Gregory, the rejection has been maintained.

**Claims 1, 3-5, 7-14, 17, 31-33, 34-35, 38-41, 42-43, 46-49, 50-51, 54-55, 59-60, 62-70, 72-84 and 91-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al (5,716,981) by itself or in view of Yapel (4,147,767) in further view of Kunz et al (5,733,925) and Westesen et al (6,197,349).**

Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such as paclitaxel, epothilone, and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as albumin, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter teaches the use of the composition to treat non-tumorigenic angiogenesis dependent diseases. See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter teaches methods of eliminating vascular obstructions in arteries and veins to prevent recurrent stenosis at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and cornary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intarticularly, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use, thus suggesting the claimed particle size of 200 nm. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent.

Example 7 teaches inserting the stent is into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

The use of albumin as the polymeric carrier is not immediately envisaged and the examiner relies on Yapel to specifically provide motivation to use albumin. Further, although it appears that Hunter implicitly teaches the delivery time, Hunter does not specify the instant administration time and the examiner relies on Kunz for this teaching. Lastly, Hunter does not specify the drug form and the examiner relies on Westesen to teach this.

Yapel teaches albumin (HAS) medicament carrier suited for intravascular injections. Yapel teaches compared to prior art polymeric carriers has advantages such as ability to administer insoluble drugs; localizes the drug in the capillaries and the drug is released at the intended sire and reduces toxic side effects which is especially useful for anti-neoplastic drugs; the absence of emboli formation wherein albumin carriers are administered; ease of preparation; nonantigenicity; capability of carrying a variety of drugs. See column 2, line 50 to column 3, lines 30.

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a

substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

Kunz et al teach methods for inhibiting stenosis following vascular trauma or disease, cancer, diseases resulting from hyperactivity or hyperplasia of somatic cells. Example 7 discloses smooth muscle proliferation in the neointima. Kunz teaches direct or targeted delivery of therapeutic agents to vascular smooth muscle cells. See column 1, lines 15-35. Inhibiting stenosis following angioplasty is contemplated. See column 3, lines 54-62. The dosage forms are preferably in biodegradable microparticulates or nanoparticulates wherein the particles are formed of a polymer-containing matrix that biodegrades. Kunz et al teach conjugating the drug with a binding protein to target the cells and reduce toxicity. Example 7 notes the toxicity of a free drug versus a conjugated drug. See column 14, lines 25-33. Kunz teaches protein-coated particulates. See column 25, line 20 to column 26, line 40. Therapeutic agents such as taxol or analogs are preferred therapeutic agents that are designed to target the cell activity without killing the cell. Taxol is taken into the cell and stabilizes the cell from further dividing. See column 4, lines 40-45 and column 13, lines 24-27. Examples of dosages include .001 to 100 mg/kg per day. See column 28, line48. For prevention of restenosis following angioplasty or an intervention that contributes to the acute proliferation of smooth muscle cells, a single pre-loading dose is given prior to or at the time of intervention with smaller chronic doses given two or three weeks after intervention. For example, a single dose may be administered about 24 hours prior to intervention, while

multiple preloading doses may be administered daily for several days prior to intervention. See column 29, lines 10-15. Delivery of the active agents may be intravenous, intra-arterial (stents), or local delivery. See column 30, lines 56-65 and examples for stent deployment. Kunz teaches single administration protocol. See column 36, lines 50-55. Example 6 teaches infusion using a balloon catheter. Administration to a carotid, femoral, and coronary artery is taught. See examples. Example 3 teaches administering the dose in less than three to five minutes. Also note example 5 and 14.

Firstly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Hunter and utilize albumin as the polymer of choice. One would have been motivated to do so with a reasonable expectation of success and similar results since Hunter suggests proteins and polypeptides such as albumin are suitable as the polymeric carrier. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hunter and Yapel and specifically utilize albumin as the polymeric carrier. One would have been motivated to do so since Yapel teaches the advantages of using albumin as the polymeric carrier including nonantigenicity, localized and targeted delivery which reduces toxicity of anti-neoplastic drugs, ease of preparation, etc.

Secondly, although it is the examiner's position that Hunter implicitly teaches the instant delivery time, i.e. by inserting a stent, it would have been obvious to administer the product in less than 30 minutes. One would have been motivated to

do so since Kunz teaches administering microparticles and nanoparticles containing an antineoplastic drug via injections and stents in a single does regimen under 30 minutes. Further, Kunz teaches the dosing cycles to treat restenosis. A skilled artisan would have reasonably expected success and similar results since both Hunter and Kunz teach the treatment of recurrent stenosis and neointimal hyperplasia with drugs that inhibit microtubule function such as taxol. Therefore, it would have been obvious to look to Kunz to determine the appropriate delivery and dosing times to treat the same disease using the same delivery vehicle and drug.

Lastly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs.

***Response to Arguments***

Applicant's arguments filed 12/22/10 have been fully considered but they are not persuasive.

Applicants argue that Hunter or Kunz fails to teach or suggest that systemically administering a therapeutic agent in nanoparticle form, coated in a coating consisting essentially of protein, in 30 minutes or less, would be effective in treating hyperplasia of non-cancerous cells in a blood vessel. The argument is not persuasive because Hunter is taught for the use of paclitaxel in treating hyperplasia and specifically teaches microspheres range from 50-nm to 500 microns depending on the particular use, thus suggesting the claimed particle size of 200 nm. See column 17, lines 25-40.

Applicant argues the teachings of Desai. However, instant rejection does not include Desai reference.

Applicant argues that Yapel does not teach a method of treating non-cancerous cell proliferation in blood vessels, or systemically administering an effective amount of a nanoparticle drug composition in less than about 30 minutes for such purpose. As discussed above, Hunter teaches the instant method of treating non-cancerous hyperplasia in the instant time frame. It is the examiner's position that Hunter implicitly teaches the delivery time. It is noted that Hunter teaches inserting a coated stent. Thus, although Hunter does not explicitly state that this is done under 30 minutes, the examiner points out that this is implicit since it takes less than 30 minute to place the catheter into a site. Further, Hunter suggests the use of protein particles such as albumin. Yapel is only relied upon to provide further motivation to utilize albumin. Therefore, applicant's argument is unpersuasive.

**Claims 36-37, 44-45, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter et al (5,716,981) by itself or in view of Yapel (4,147,767) in view of) Kunz et al (5,733,925) and Westesen et al (6,197,349) in further in view of Marx (Circ. Res. Vol. 76, pp. 412-417, 1995).**

The disclosures of Hunter, Yapel, Kunz, and Westesen have been set forth above.

The references do not teach the specific use of rapamycin as the antiproliferative agent.

Marx teaches rapamycin is an inhibitor of smooth muscle cells in the abnormal proliferation of restenosis. See abstract.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of the above references and utilize the instantly claimed drugs. One would have been motivated to do so with a reasonable expectation of success since Marx teaches the rapamycin is a smooth cell inhibitor useful in treating restenosis. The selection of a specific drug is considered prima facie obvious to a skilled artisan in the art.

***Response to Arguments***

Applicant's arguments filed 12/22/10 have been fully considered but they are not persuasive.

Applicant argues the merits of Hunter, Yapel, Kunz, and Westesen, which have been addressed above and incorporated herein. It is argued that Marx does not cure the deficiencies of other references. Since applicant has not addressed the instant rejection specifically, the rejection is maintained for the reasons set forth in the rejection.

***Double Patenting***

**Claims 1, 3-14, 17, 31-33, 38-41, 46-49, 54-55, 59-60, 62-70, 72-84 and 91-96 over claims 1-7, 11-20, 44-45 of 11/359286 respectively in view of Hunter et al and Westesen.**

The instant application is directed to a method of treating hyperplasia in the blood vessels and a method of reducing proliferation in vascular procedures comprising

administering an antineoplastic; antiproliferative; or angiogenesis inhibitor coated with a protein.

Copending application '286 is directed to a method of treating a proliferative disease in an individual comprising administering to the individual: a) an effective amount of a composition comprising nanoparticles comprising a taxane and an albumin, and b) an effective amount of at least one other chemotherapeutic agent, wherein said chemotherapeutic agent is selected from the group consisting of antimetabolites, platinum-based agents, alkylating agents, tyrosine kinase inhibitors, anthracycline antibiotics, vinca alkloids, proteasome inhibitors, macrolides, and topoisomerase inhibitors. Dependent claims are directed to rapamycin, albumin, the instant route of administration; and particle size.

The copending application does not specify the proliferative disease. Hunter et al teach anti-angiogenic compositions comprising an anti-angiogenic factor and a polymeric carrier and methods of its use. See abstract and column 3, lines 40-45. Preferably the active compound is a compound that disrupts microtubule function such as paclitaxel, epothilone, and etc. see column 3, lines 60-65. The polymeric carrier may be chosen from a carbohydrate, protein, or polypeptide such as albumin, collagen, and gelatin. See column 18, lines 15-30. Hunter teaches using the composition to coat a stent which is inserted into the body. Delivery may be done through via expandable catheters. See column 4, lines 24-30 and column 22. Hunter teaches the use of the composition to treat non-tumorigenic angiogenesis dependent diseases. See column 5, lines 44-46 and column 36, lines 9-15. Specifically Hunter

teaches methods of eliminating vascular obstructions in arteries and veins to prevent recurrent stenosis at the site of failed angioplasty and to treat post surgical narrowing. Suitable sites of the stent include iliac, renal, and femoral, and cornary arteries. See column 25, lines 48-67. Hunter teaches treating neointimal hyperplasia wherein a stent is coated with the composition and inserted onto the arteries. See column 36, lines 1-20. The composition may be further administered intarticularly, intravenously, etc. see column 37, line 67 to column 38, lines 1-10. The microspheres range from 50-nm to 500 microns depending on the particular use. See column 17, lines 25-40. Anti-angiogenic factors may be linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. See column 17, lines 1-5. Hunter teaches administering the anti-angiogenic composition using a stent. Example 7 teaches inserting the stent is into a rat. It should be noted that insertion of the stent would meet the instant delivery time since the composition is delivered to the site in less than 30 minutes (the time it takes to insert a stent is less than 30 minutes).

Westesen et al teach nanoparticles containing various poorly water-soluble drugs. See abstract. Westesen teaches the use of an amorphous form of the drug to provide for better solubility and bioavailability of poorly water-soluble drugs than utilizing a crystalline form. See column 5, lines 45-56. Generally amorphous forms of a substance exhibit a higher solubility and a faster dissolution than the crystals forms since they do not require lattice energy.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the copending application and Hunter to arrive at the instantly claimed invention of treating hyperplasia of blood vessels and deliver the composition in less than 30 minutes. One would have been motivated to do so since Hunter teaches neointimal hyperplasia is a proliferative disease that can be treated with anti-neoplastic drugs that disrupt microtubule function. Therefore, although the copending applicationdo not specify treating hyperplasia, instant application and copending applications are directed to similar subject matter since hyperplasia is a proliferative disease.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an amorphous drug form. One would have been motivated to do so since Westesen teaches the use of an amorphous form for better solubility and bioavailability of poorly water-soluble drugs.

This is a provisional obviousness-type double patenting rejection.

***Response to Arguments***

Applicants request that the provisional rejections be held in abeyance until the office has made a determination of allowable subject matter. Since applicants did not argue the merits of the rejection and since there are no allowable claims, the rejection of record has been maintained.

The following rejection has been withdrawn in light of the statement that the copending application 11/594417 has been abandoned.

**1, 3-5, 7-14, 17, 31-33, 38-41, 46-49, 54-55, 59-60, 62-70, 72-84 and 91-96 over claims 1-2, 5-18 11/594417.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611